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OP0069

PERFORMANCE OF AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) COMBINED RESPONSE INDEX IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS (CRISS) SCORE IN PHASE 2 TRIAL OF LENABASUM IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS (DCSS)

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Background: Change in modified Rodnan skin score (mRSS) has been used as primary efficacy outcome in at least 13 failed controlled studies in dcSSc. In 2016, the CRISS score was provisionally accepted by ACR as a primary efficacy outcome for clinical trials in dcSSc. Its performance as a primary efficacy outcome has not been tested in a clinical trial.

Objectives: To evaluate performance of ACR CRISS outcome measure in the lenabasum Phase 2 study in dcSSc, the first study in which it was used prospectively as the primary efficacy outcome.

Methods: The Phase 2 study JBT101-SSc-001 (NCT02465437) included a 16-week, double-blinded, randomized, placebo-controlled Part A followed by an open-label extension (OLE). ACR CRISS score is calculated from a weighted exponential formula that includes change in mRSS, Patient Global Assessment (PtGA), HAQ-DI, Physician Global Assessment (MDGA), and FVC% predicted. Spearman correlations were determined for: pairs of core items at Baseline; change in pairs of core items; and change in a given core item and calculated ACR CRISS score. Median ACR CRISS scores were determined in subjects with different levels of improvement in patient-reported outcomes (PROs).

Results: Correlations among pairs of CRISS core items at baseline and change in core items were all < 0.80 at 4 and 12 months. The strongest correlations ($r \geq 0.60$, $P \leq 0.0001$) for core items at baseline were between PtGA and HAQ-DI, HAQ-DI and MDGA, and PtGA and MDGA. The strongest correlations ($r \geq 0.50$, $P \leq 0.001$) for changes in pairs of core items were between PtGA and HAQ-DI, HAQ-DI and MDGA, and MDGA and mRSS, all others were ≤ 0.30 (Table 1). Correlations between change in each core item and ACR CRISS score were all statistically significant, $p \leq 0.05$ at both 4 and 12 months and very strong for change in mRSS and ACR CRISS (Table 1).

Median ACR CRISS scores increased with increasing levels of improvement in PROs that were core items (HAQ-DI and PtGA) and even PROs (PROMIS-29 domains) that were not core items. Median ACR CRISS score associated with improvement in HAQ-DI at least -0.250 points was 0.82 and associated with at least 1-point improvement in PtGA was 0.53 at 12 months.

Table 1. Correlation of ACR CRISS with Change in Core Item, r

Time	Correlation of ACR CRISS with Change in Core Item, r				
	mRSS	PtGA	HAQ-DI	MDGA	FVC% predicted
4 months	-0.91	-0.37	-0.45	-0.66	0.38
12 months	-0.76	-0.38	-0.39	-0.38	0.54

Conclusion: In the context of the lenabasum Phase 2 clinical trial, ACR CRISS core items at baseline and change in ACR core items were not redundant ($r < 0.80$). Change in each core item correlated with ACR CRISS score, indicating each contributed to the score at both 4 and 12 months. The 12-month median ACR CRISS score was higher in subjects with greater levels of improvement in PROs, even PRO that were not core items, showing that ACR CRISS score reflects long-term clinical benefit in how the patient feels and functions. These data provide preliminary evaluation of the ACR CRISS score as a clinical trial endpoint in dcSSc.

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WEDNESDAY, 12 JUNE 2019

Bringing digital health care solutions to patients

OP0070-PARE

GEOCACHING AS AN ENCOURAGEMENT FOR BEING ACTIVE

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Background: The Finnish Rheumatism Association and Novartis started a project in 2017 to energise our local associations, members and their families by adapting an active lifestyle. Geocaching is a fun, family-friendly way to exercise both mind and body. It is for everybody to enjoy.

Geocaching is an outdoor recreational activity, in which participants use a Global Positioning System (GPS) receiver or mobile device and other navigational techniques to hide and seek containers, called "geocaches" or "caches", at specific locations marked by coordinates all over the world.

There are about three million geocaches hidden around the world. A typical cache is a small waterproof container containing a logbook and sometimes a pen or pencil. The geocacher signs the log with their established code name and dates it to prove that they found the cache. After signing the log, the cache must be placed back exactly where it was found.

Objectives: The main goal of the project was to hide 70 new caches all over Finland to create an enjoyable experience for other geocachers. Those caches were named "Reumageo" at the beginning of the cachename. For all the associations that were involved in this project received money allocated to sport and physical activity out of the 15,000 euro project budget. The project ended on 12 October 2018, and all logged caches were included in the game.

Methods: We started our project by training association representatives. The training included the basics of geocaching: how to find caches, how to hide your cache and create your cache page, different geocachetypes and everything you should know geocaching. The trained representatives told about geocaching in their own associations, and they were responsible for creating at least 2-3 new caches and handling the new caches. The main idea was that when you have found about 15-20 caches you would start to hide your own caches. Together with local associations our aim was to create 70 caches all over Finland to celebrate the 70-year-old Finnish Rheumatism Association.

Outdoor geocaching adventure starts indoors with preparation and online research. You need a Global Positioning System (GPS) receiver or a mobile device, your own account at the site geocaching.com. The site offers a completely free access to the caching data and all the site features. The site offers also a "premium" member status to access certain features. You can also download the Geocaching intro app onto your smartphone, like Geocaching.

Results: There were 43 members from 30 local associations in Oulu, Mikkeli, Helsinki and Turku in these geocaching trainings. All these members are suffering from rheumatic and other musculoskeletal diseases (RMDs) and work as volunteers for sport and physical activity, and now for geocaching. By 12 October 2018 there were 48 reumageocaches made by 13 local associations. The caches were logged 6593 times. So local associations earned 173-4303 euros each to be used for promoting sport and physical activity programmes and active lifestyles.

Conclusion: Promoting an active lifestyle is part of the health and wellbeing policy in The Finnish Rheumatism Association. The goal is to encourage people of all ages to stay healthy by getting enough exercise.

The geocaching project shows that it is easy to some of local associations to start projects like this. Some associations thought that it is too difficult to learn new methods especially when their members are elderly people. Geocaching is increasingly popular, inclusive, a fun and healthy pastime for individuals of all ages. It is also great for groups like local associations, families, friends, and youth groups working as teams. Those local associations that were involved in this project received a great budget for their local sport and physical activity programmes. It is great to see something evolving from the beginning and come into being.

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Cartilage, synovium and bone

OP0071

REVEALING THE LINK BETWEEN OSTEOARTHRITIS DEVELOPMENT AND MESENCHYMAL STEM CELL SENEESCENCE

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Background: Tissue accumulation of p16^{INK4A}-positive senescent cells is associated with age-related disorders such as osteoarthritis (OA). These senescent cells induce a tissue loss of function through a particular secretory phenotype called SASP (senescence-associated secretory phenotype).

Objectives: Links between OA onset and cellular senescence remain poorly detailed. We wanted to determine the localization of articular senescent cells in *in vivo* OA mouse models and study the involvement of mesenchymal stem cells (MSC) senescence in OA pathogenesis.

Methods: Wild-type mice C57BL/6, SAMP8/R1 (senescence accelerated mouse-prone and resistant), transgenic p16^{INK4A} +Luc and p16^{INK4A} Luc/Luc were used. Experimental OA was induced by intraarticular injections of collagenase (CIOA). Cartilage, synovial tissue and subchondral bone were analyzed by histology, RT-qPCR and micro-tomography. MSCs come from healthy human donors and primary chondrocytes from OA patients.

Results: (1) CIOA was induced in senescence-driven luciferase transgenic mice. Under CCD camera, a peak in luminescence was detected at day 24 post-injection revealing the presence of senescent cells in the joint. Remarkably, articular senescence is not only a marker of the pathology but contributes to OA onset: mice deficient in p16^{INK4A}, a main senescence-driving known cell cycle inhibitor, were partially protected against CIOA. These results were confirmed in C57BL/6 mice after CIOA by showing an increase in gene expression for senescence, catabolic and inflammatory markers in the synovial tissue preceding cartilage degradation.

(2) MSCs found in synovial, cartilage, fat pad and bone marrow participate in joint homeostasis. Because MSC are proposed to be at the root of OA development, we hypothesize that cellular senescence onset in these progenitor cells would be a possible etiological factor for OA. We have established an *in vitro* p16^{INK4A}-induced senescence model on human primary MSC: their intrinsic properties such as self-renewing are altered during senescence onset. Furthermore, in co-culture conditions with chondrocytes from OA patients, senescent MSC lost their extrinsic chondroprotective properties.

(3) To *in vivo* challenge these findings, we rely on the mouse model of accelerated senescence SAMP8, which develop spontaneous OA at the age of 6 months with cartilage degradation, synovial hypertrophy, osteophytosis and subchondral bone remodeling associated to meniscal calcification. Isolated MSC from these mice express senescence but non-inflammatory markers (p16^{INK4A}, p21waf1, MMP13, TGF-β1). Remarkably, intra-articular injection of these isolated SAMP8-derived MSC compared to SAMR1-derived control MSC, in young wild-type C57BL/6 mice, was sufficient by its own, to induce significant articular cartilage degradation (OA score of 12.2 ± 1.5 vs 6.1 ± 3.5 for SAMP8 and SAMR1 MSC respectively. p < 0.05).

Conclusion: p16^{INK4A}-induced cellular senescence in MSC played a causative role in cartilage loss of function and OA pathogenesis. *In vitro*, senescent MSC show

altered intrinsic and extrinsic supportive tissue functions. *In vivo*, intra-articular injection of senescent MSC was sufficient to induce cartilage degradation. Specific targeting of such deleterious senescent cells could be an innovating and promising treatment in OA.

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OP0072

INHIBITION OF CLK2 AND DYRK1A BY SM04690 AS A NOVEL MOLECULAR REGULATOR OF WNT SIGNALING, CHONDROGENESIS, AND INFLAMMATION, A POTENTIAL DISEASE-MODIFYING TREATMENT FOR KNEE OSTEOARTHRITIS

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Background: In the synovial joint, Wnt pathway upregulation contributes to osteoarthritis (OA) by increasing osteocyte differentiation, cartilage thinning, and inflammation. SM04690, a novel small molecule, has previously demonstrated potential OA disease-modifying effects through Wnt pathway inhibition *in vitro* and *in vivo*.

Objectives: To elucidate the novel mechanism of action for SM04690 on Wnt pathway inhibition, chondrocyte differentiation, and anti-inflammation.

Methods: Wnt pathway activity was measured using a cell-based TCF/LEF luciferase reporter in SW480 colon cancer cells. A kinome screen (318 kinases) was performed. The effects of SM04690 on protein phosphorylation of serine and arginine rich splicing factors (SRSF proteins), Sirt1, and FoxO1 in hMSCs, chondrocytes, and synovial fibroblasts were measured by Western blot. The effects of SM04690 and siRNA knockdown (KD) on chondrogenic and Wnt pathway gene expression were measured by NanoString gene expression panels and effects on LPS-induced inflammatory cytokines (IL-6, IL-8, TNF-α) in BEAS-2B cells were measured by qPCR and ELISA. *In vivo*, the pharmacodynamic effects of SM04690 were evaluated in monosodium iodoacetate injection-induced and anterior cruciate ligament transection with partial medial meniscectomy rat knee OA models in which a single intra-articular SM04690 (0.1 μg, 0.3 μg, 1.0 μg) or vehicle injection was administered. Cartilage was isolated at Day 10 and 35; phosphorylation and expression of SRSF proteins, Sirt1, FoxO1, STAT3, and NF-κB were measured by Western blot.

Results: SM04690 was a potent (EC₅₀ = 11 nM) inhibitor of Wnt signaling. Cdc-like kinases (CLKs) and dual-specificity tyrosine kinase (DYRK1A) were identified as molecular targets of SM04690. In hMSCs and chondrocytes, compared to DMSO, SM04690 potently inhibited CLK-mediated phosphorylation of SRSF proteins. SM04690 also inhibited DYRK1A-mediated Sirt1 and FoxO1 phosphorylation, thus increasing total and nuclear FoxO1 levels. Compared to siRNA control, DYRK1A/CLK2 dual KD increased expression of chondrogenic genes (*COL2A1*, *ACAN*, *COMP*, *CD44* [all *P* < 0.05]). CLK2 and DYRK1A KDs each inhibited Wnt pathway genes (*AXIN2*, *TCF7*, *TCF4*, *LRP5*, *FZD6*, *FZD7*, *PITX2* [all *P* < 0.05]) with no effects on β-catenin levels, compared to siRNA control. In synovial fibroblasts, compared to DMSO, SM04690 decreased phosphorylation of NF-κB and STAT3. In BEAS-2B cells, compared to siRNA control, DYRK1A KD inhibited inflammatory cytokine production (IL-6, IL-8, TNF-α [all *P* < 0.05]), while DYRK1A/CLK2 dual KD enhanced anti-inflammatory effects of DYRK1A KD. In cartilage from rat OA models, compared to vehicle, SM04690 inhibited phosphorylation of SRSF proteins, Sirt1, FoxO1, and STAT3, as well as expression of NF-κB.

Representation of dual mechanism of action of SM04690

Figure 1. Schematic representation of SM04690's proposed mechanism of action via CLK2 and DYRK1A inhibition in OA